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Does administration of 800 mg intravenous ibuprofen reduce post-surgical pain within 24-28 hours?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not administration of 800 mg IV ibuprofen reduces post-surgical pain within 24-28 hours.

Study Design: A systematic review of three randomized, double blind, placebo-controlled studies.

Data Sources: All studies were published in English during or after the year 2010. All articles were obtained from peer reviewed journals and databases using PubMed and CINAHL Plus. Selection was determined based on the relevance to the clinical question.

Outcomes Measured: All three studies aimed to measure the efficacy of IV ibuprofen on the reduction of post-operative pain at rest and with movement by 24-28 hours. This was done using a visual analog scale (VAS), area under the curve (AUC), and mean difference between groups.

Results: In the randomized control trial (RCT) performed by Singla et al. there was a significant difference (p-value <0.001) in post-operative pain reduction between the experimental and control group. There was a least square mean difference calculated as -269 at rest and -321.1 with movement. Kayhan et al. performed a RCT that found a statistically significant decrease in pain reduction between the experimental and control groups (p-value < 0.001). A mean difference of -4.01 at rest and -10.22 with movement was calculated between groups. The RCT performed by Martinez et al. determined there to be a statistically significant decrease in pain between the experimental and control group. There was a mean difference of 0.08 at rest and 0.24 with movement.

Conclusion: All three studies demonstrated that 800 mg IV ibuprofen provides a statistically significant decrease in severity of post-surgical pain within 24-28 hours.

Key Words: Intravenous, ibuprofen, postoperative, pain

Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug, NSAID, currently used as an "everyday" reliever for a range of pains including muscle aches, arthritis, headaches, menstrual cramps, and dental pain. It is a non-selective inhibitor of the COX-1 and COX-2 enzyme that promotes the sensitization of pain and decreases inflammation[1]. Alternatively, opioids such as morphine are used for post-surgical pain management and provide no benefit to the underlying disease process. Therefore, using NSAIDs as adjunctive therapy for post-surgical pain management may help to promote resolution of inflammation, pain, and overall post-surgical healing.[1]

In 2017, an opioid epidemic was classified by the U.S Department of Health & Human Services as a public health emergency. Research shows that there were 47,000 deaths in 2018 secondary to prescription opioids. Of these, 32% involved prescription medications of the individual.[2] Although opioid analgesics are the basis of care for post-operative patients, they are being over-prescribed, have the potential for misuse, and can lead to severe adverse reactions.[1] Adjunctive medications including ibuprofen can be used to lessen the side effects and help decrease the total dose of opioids required.

Surgical care is a highly demanded specialty requiring around the clock care and medical attention. There are 51 million inpatient surgeries requiring opioid analgesia in the U.S. every year.[3] In the U.S., more than 60% of patients who experienced moderate-severe post-surgical pain received morphine as the treatment of choice.[4] The U.S. typically spends $560-$635 billion annually trying to treat pain, with a majority of patients requiring in-patient post-surgical care.[5] Current studies lack information comparing the cost comparison of IV ibuprofen versus the current mainstay of opioid analgesia post-operatively. Typically, the cost of IV ibuprofen 10

mg/ml is $876 for 6 mL.[6] More information needs to be provided about standard cost of IV ibuprofen treatment in the inpatient setting.

Studies are currently looking at the efficacy and safety of the use of IV ibuprofen in acute post-surgical cases. Overall data suggests similar safety profiles between IV and oral ibuprofen. What is unknown is how IV administration would be tolerated in prolonged therapies.[1] Research is looking into the efficacy of a multimodal approach to post-operative pain to achieve pain relief while decreasing and minimizing the total amount of opioids required. This systematic review aims to determine if IV ibuprofen can be an efficient medication to be used in the post-surgical setting for pain management.

Objective

The objective of this selective EBM review is determining whether or not administration of 800 mg IV ibuprofen reduces post-surgical pain within 24-28 hours.

Methods

Three randomized, placebo-controlled double-blind studies from peer-reviewed journals were selected for this review. The studies in this review were searched, by myself, using PubMed and CINAHL databases with the keywords “intravenous”, “ibuprofen”, “postoperative”, and “pain”. Studies were selected for the review based on relevance to the clinical question, if the results were measured by Patient-Oriented Evidence that Matters (POEMs) and if they met the inclusion criteria for the review. Inclusion criteria that were required included randomized control trial published during or after 2010, adult patients, English language, and primary research. Exclusion criteria consisted of studies published before 2010 and patients under the age of 18 years old. A summary of the criteria for each study can be further reviewed in Table 1.

In all three studies, the population being reviewed are patients 18 years or older undergoing elective surgical care, requiring hospitalization and need for IV pain management. All three studies evaluated the use of 800 mg IV ibuprofen, with rescue IV morphine, as a post-surgical analgesia intervention. In two of the articles, the use of IV ibuprofen was compared to the use of IV saline. In the third study, IV acetaminophen was used as the control group. Differences in medication administration are highlighted in Table 1, as timing of infusions varied. These studies used a visual analog scale (VAS) to gather information from patients on pain level. To evaluate efficacy of IV ibuprofen on reduction of post-surgical pain by 24-28 hours, these studies used area under the curve (AUC), mean difference between groups, and p-values.

Outcomes Measured

The outcome measured in all three studies looked at the efficacy of IV ibuprofen and whether or not it can reduce post-surgical pain. The data was collected by VAS to assess pain at selected hourly intervals at rest and with movement. The VAS was a self-assessment that ranked pain from 0 to 100 (0= no pain and 100= the worst pain imaginable).[4,7] The scale is a continuous line from 0-100 without intermediate descriptors to avoid unclear responses. At each time check, the patient would mark a line on the VAS to indicate their pain at that time period. In the study by Martinez et al. the VAS was on a 0-10 scale instead, but instructions were the same for participants.[8] For the purpose of this review, a common time interval of 24-28 hours was used to compare pain levels. In order for the patients to participate in the VAS, they were required to be coherent and able to comply to study procedures after recovery from sedation. To analyze the data and qualify the outcomes, the studies used mean difference between groups, AUC and p-values to determine the significance.[4,7]

Table 1. Demographics & Characteristics of Included Studies

Study	Type	#Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Singla, Rock, Pavliv[4] (2010)	Double blind RCT	185	24-80	Scheduled for elective hip or knee replacement, reconstruction or arthroplasty with need for post-op IV morphine, hospital stay > 28 hours	<18 or >80 years old, pregnant or nursing, use of analgesics less than 12 hours prior to surgery, pre-existing dependence on narcotics or opioids, allergy to NSAIDS, taking CI medication	1	800 mg IV ibuprofen q6 hours (at start of anesthesia) up to 28 hours post-op Vs IV saline solution *Both with access to morphine
Kayhan, Sanli, Ozgul, Kirteke, Yologlu[7] (2018)	Double blind RCT	80	18-65	Age 18-65 years old, obese, ASA physical status II-III, scheduled for laparoscopic sleeve gastrectomy or Roux-en-y gastric bypass	Hepatic dysfunction, renal insufficiency, hx of GI bleed, anticoagulant use or ACE, opioids addiction, hx of allergy to drugs in study, patients unable to cooperate	6	800 mg IV ibuprofen 30 min prior to closure and q6 hours for 24 hours Vs 1 g IV acetaminophen 30 min prior to closure and q 6 hours up to 24 hours *Both with access to morphine
Martinez, Rodriguez, Roca, Ruiz[8] (2016)	Double blind RCT	206	18-80	18-80 years old, scheduled for elective orthopedic or abdominal surgery requiring anesthesia and post-op narcotics, hospital stay >24 hours	GI, cardiac, liver, or renal disease, taking CI medications, bleeding disorders, pregnant/nursing, dependence of narcotics, hx of allergy to study medications. Severe trauma w/in 30 days	All orthopedic cases w/d. Only 122 cases analyzed for abdominal surgery	800 mg IV ibuprofen q6 hours for 24 hours Vs IV saline solution *Both with access to morphine

Results

Singla et al. conducted a randomized double-blind placebo-controlled trial to determine if administration of IV ibuprofen can significantly decrease pain for adult patients undergoing orthopedic surgical procedures. The study was conducted at eight hospitals in the U.S and South Africa. Patients ages 18 to 80 scheduled to have orthopedic surgery requiring a hospital stay and need for morphine analgesia for at least 28 hours were considered for the study.[4] Further inclusion and exclusion requirements are located in Table 1. A total of 185 patients were randomized to receive either 800 mg IV-ibuprofen (N=99) or the placebo (N= 86) every six hours, with the first dose administered pre-operatively at the induction of anesthesia. The remainder of the doses were scheduled every 6 hours for the next 24 hours. All patients had access to IV morphine for rescue analgesia. VAS was used as a self -assessment of pain at rest (VASR) and movement (VASM) from hour 6-28 (post-operative period) after receiving the first dose at the induction of anesthesia.[4] This self-assessment was collected from hour 6-28 at 6-hour intervals. VAS was a standard 100-mm scale. Efficacy was measured using AUC from 6 to 28 hours for the VAS assessment with rest and movement (Table 2).[4] P-value and least squares (LS) means difference (95% CI) was calculated from analysis of covariance (ANCOVA) model (Table 3). [4] Statistical analysis determined there to be a significant decrease in pain of the experimental group compared to the control group.

Table 2. VAS Mean Scores Expressed as AUC (standard deviation) with Movement and Rest from Hours 6-28[4]

	Experimental	**Control Group**
Pain at Rest (6-28 hours)	620.8 (401.0)	910.9 (424.3)
Pain with Movement (6-28 hours)	970.1 (422.2)	1,307.8 (388.7)

Table 3. Change in Pain Level Expressed as LS Means Difference (95% CI) Between Experimental and Control Group[4]

	Mean Difference	P-Value
Pain at Rest	-269.0 (-386.8, -151.2)	*<0.001
Pain with Movement	-321.1 (-436.7, -205.4)	*<0.001

*=Statistically Significant (P<0.05)

Kayhan et al. conducted a randomized double-blind placebo-controlled study comparing the use of IV ibuprofen to IV acetaminophen. There were 80 subjects aged 18-65 (ASA physical status II-III) undergoing laparoscopic sleeve gastrectomy or laparoscopic Roux-en-Y gastric bypass surgery that participated in the study at a university hospital.[7] There were five subjects lost to follow-up in the control group; four subjects secondary to protocol violations and one secondary to allergic reaction. One patient was excluded from the analysis of the experimental group secondary to post-operative complications. These patients were randomly selected to receive 800 mg IV ibuprofen (N=35) or the control 1 g IV acetaminophen (N=39) every 6 hours for the first 24 hours following surgery.[7] In addition, patient-controlled analgesia with morphine was administered if VAS was ≥ 40 when patients completed the VAS at the pre-determined time intervals.[7] At these pre-determined intervals every 6 hours, the patient would complete a VAS (0= no pain to 100= the worst pain imaginable) to qualify pain.[7] Patients were told to assess their pain at rest (sitting position) and with movement (standing from a sitting position) every 6 hours. To determine overall pain at the various time points, the AUC was analyzed over the first 24 hours to provide mean VAS scores for both the experimental and control groups with rest and movement (Table 4).[7] Quantitative data was calculated using least squares mean difference with 95% confidence interval. In addition, the Analysis of Variance (ANOVA) with Bonferroni multiple comparisons test determined that there was a significant difference between the pain reduction of the experimental and control groups (Table 5).[7]

Table 4. VAS Scores Expressed as Mean ± SD (Standard Deviation) Over a 24-Hour Period at Rest and With Movement[7]

	Experimental	Control Group
Pain at Rest (1-24 hours)	28.73 ±19.53	32.34 ± 22.43
Pain with Movement (1-24 hours)	35.53±20.22	43.20±22.23

Table 5. Change in Pain Level Measured as Mean Difference Between Experimental and Control Groups[7]

	Mean Difference	P-Value
Pain at Rest	-4.01 (-6.17, -1.84)	*<0.001
Pain with Movement	-10.22 (-12.53, -7.92)	*<0.001

*=Statistically Significant (P<0.05)

Martinez et al. conducted a randomized control trial designed to evaluate the efficacy of IV-ibuprofen for the treatment of pain in post-operative elective abdominal and orthopedic surgery in adult patients.[8] The study was conducted at a total of nine Spanish hospitals in the inpatient setting. Further discussion of inclusion and exclusion criteria are in Table 1. There were 206 patients assigned to receive either 800 mg IV ibuprofen or a placebo every 6 hours. All patients had access to morphine through a patient controlled analgesic pump. Ultimately, the analysis was limited to abdominal surgeries due to limited orthopedic enrollment. Therefore, the experimental group (N=72) and placebo group (N=63) all underwent abdominal surgery.[8] The first dose of the study drug was administered upon skin closure indicating "Hour 0". Subsequent doses were administered every 6 hours for a total of 24 hours. All patients had access to a 1 mg bolus dose of IV morphine, if desired, upon discharge from the operating room. Subsequent dosing would only be permitted by the patient's physician if adequate pain control was not achieved. VAS was performed at each six-hour interval over the 24-hour period and reported as mean ± standard error of the mean (SEM; Table 6).[8] Mean difference was used to analyze the

difference in pain levels between groups (Table 7). Statistical significance calculated with the Log-Rank test found a larger decrease in pain level in the experimental versus control group.[8]

Table 6. VAS Scores Expressed as Mean ± SEM Over 24-Hour Period at Rest and With Movement[8]

	Experimental		**Control Group**	
	Hour 0	Hour 24	Hour 0	Hour 24
Pain at Rest	3.34 ±0.35	0.86±0.24	4.68 ± 0.40	2.12±0.42
Pain with Movement (1-24 hours)	4.32±0.36	1.90±0.30	5.56±0.42	3.38±0.44

Table 7. Change in Pain Level Measured as Mean Difference Between Experimental and Control Groups[8]

	Mean Difference	**P-Value**
Pain at Rest	0.08	*<0.001
Pain with Movement	0.24	*<0.001

*=Statistically Significant (P<0.05)

Discussion

Opioid medications continue to be the mainstay of treatment for post-surgical pain. Due to the recent opioid epidemic, more research has been conducted in effort to use adjuvant medication in post-surgical analgesia to reduce levels of morphine consumption. Caldolor, an intravenous form of ibuprofen was first approved on June 11, 2009 for the adult population and November 20, 2015 for the pediatric population.[9] According to the Food and Drug Administration (FDA), NSAIDS and specifically Caldolor, have a serious risk of cardiovascular and gastrointestinal events.[10] Furthermore, it is contraindicated in the setting of peri-operative pain for coronary bypass graft surgery. Additionally, NSAIDs may also diminish the effects of

ACE- inhibitors. Adverse reactions may include nausea, flatulence, vomiting, headache, hemorrhage, and dizziness.[10] Opioids also offer their share of adverse effects including respiratory depression, sedation, allergic reactions, and gastrointestinal effects.[1] Despite the potential for adverse effects, oral ibuprofen is a trusted anti-inflammatory and analgesic medication. Until recently, ibuprofen has not been considered in the inpatient setting due to lack of available parenteral formulation and difficulty for IV production due to its lipophilic properties.[1] With an FDA approved intravenous formulation, research is looking at its use in reduction of post-surgical pain. This is due to the mechanism of action working peripherally and centrally to reduce pain and inflammation, whereas morphine reduces pain but has no improvement to the underlying disease process.[1]

All three studies looked to answer the question if the use of IV ibuprofen can be used to reduce post-surgical pain. In the study by Kayhan et al. there was a statistically significant decrease in pain with IV ibuprofen as confirmed with p-value ($p < 0.001$).[7] With a mean change of 4 at rest and 10 with movement, a patient could feel a significance in pain reduction. In Martinez et al. there was a statistically significant change in pain reduction between both experimental and control groups as determined by the p value ($p<0.001$).[8] Based on patient concern, a change of 0.08 at rest and 0.24 with movement would not produce a noticeable change on a 10 cm VAS scale. In addition, Singla et al. also found a statistically significant decrease in pain with the experimental group, confirmed by p-value. There was a 25% decrease in the mean AUC-VASM and a 31.8% decrease in the mean AUC-VASR.[4] In regard to the patient, a decrease this level would be noticed by a patient.

In regard to limitations, there are a few concerns to address with the studies. First, there was a difference in the VAS scales and analysis between trials. Being able to compare a VAS of

the same numerical length would have allowed for more efficient comparison. Having a larger scale (0-100) could have allowed the patient to report a larger change in pain scale compared to someone limited to a smaller scale (0-10). In addition, Martinez et al. excluded the entire orthopedic group from the efficacy analysis due to reduced sample size. This impacted the overall VAS mean resulting in lower values and, ultimately, a smaller difference between means.[8] Orthopedic surgery is reported to produce some of the highest ranked post-surgical pain, which would have been beneficial to the generalizability of the study.[8] In combination, these three articles studied participants of abdominal and orthopedic surgeries. Although these are some of the most common procedures, these articles lack a variety of surgical specialties that also require post-surgical care.

This review, in particular, limits the discussion of IV Ibuprofen's safety profile. The safety profile is outside the scope of the review, but it would be beneficial to inform the audience on the drug's side effects. Drug reactions may influence how the patient rates their pain or it may result in participants withdrawing from the study. Additionally, this review does not focus on the amount of morphine that was used. The review is patient oriented and only focuses on the effects of IV Ibuprofen. It does not focus on statistical changes with the overall amount of morphine to determine if there was a statistically significant reduction.

Conclusions

In summary, the use of 800 mg IV-ibuprofen reduces post-surgical pain within 24-28 hours. All three studies showed a statistically significant reduction in post-surgical pain with the experimental group compared to the placebo group. Although statistically significant, Martinez et al. provided a decrease that would likely be undetected by a patient. This value was presumed

to be due to the large exclusion of an entire category of participants.[8] With the strength of the additional studies, it provides a clearer answer to the proposed efficacy of IV ibuprofen.

Future studies should try to increase generalizability by studying a variety of surgical specialties, as well as the use of pediatric patients. To add, more research needs to be done to evaluate the cost of IV Ibuprofen and if this form of pain management will be cost effective. Such a large difference in cost compared to the mainstay treatment will deter health professionals and insurance companies from using IV Ibuprofen to treat post-operative pain. Therefore, more research needs to be conducted to lower the cost of the drug to be beneficial to the patient and payers. Additionally, research should be done to analyze the reduction of morphine use found within these studies and those to come. Although not a direct patient-oriented concern, opioids do have the risk of causing adverse effects on patients and dependency.[1] Future review may show a statistically significant decrease in amount of morphine used with the addition of adjuvant IV ibuprofen. In this case it will help to strengthen the argument that IV-ibuprofen should be used in post-surgical analgesia care. In sum, 800 mg IV-ibuprofen should be considered a new mainstay treatment as part of the post-surgical pain reduction treatment.

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